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(54) Abstract Title
METERED DOSE INHALER FOR SALMETEROL

(57) A metered dose inhaler possessing a canister containing salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant, a dose metering valve, and an actuator, the actuator body possessing a nozzle block for receiving the dose metering valve and defining an exit channel whose diameter at its narrowest point is between 0.2 and 0.4mm and whose length is between 1 and 2mm and/or the ration of the diameter of the exit channel at its narrowest point to its length is between 3.5:1 and 10:1. The drug suspension may contain fluticasone propionate. The dose metering valve possesses a chamber of volume between 20-100µl. The exit channel may have a variable diameter along its length be tapered or possess a constriction and connects to an exit chamber at a 50-90° angle. The inhaler is intended to optimize the fine particle mass (FPM) of the dose.

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FIGURE 1

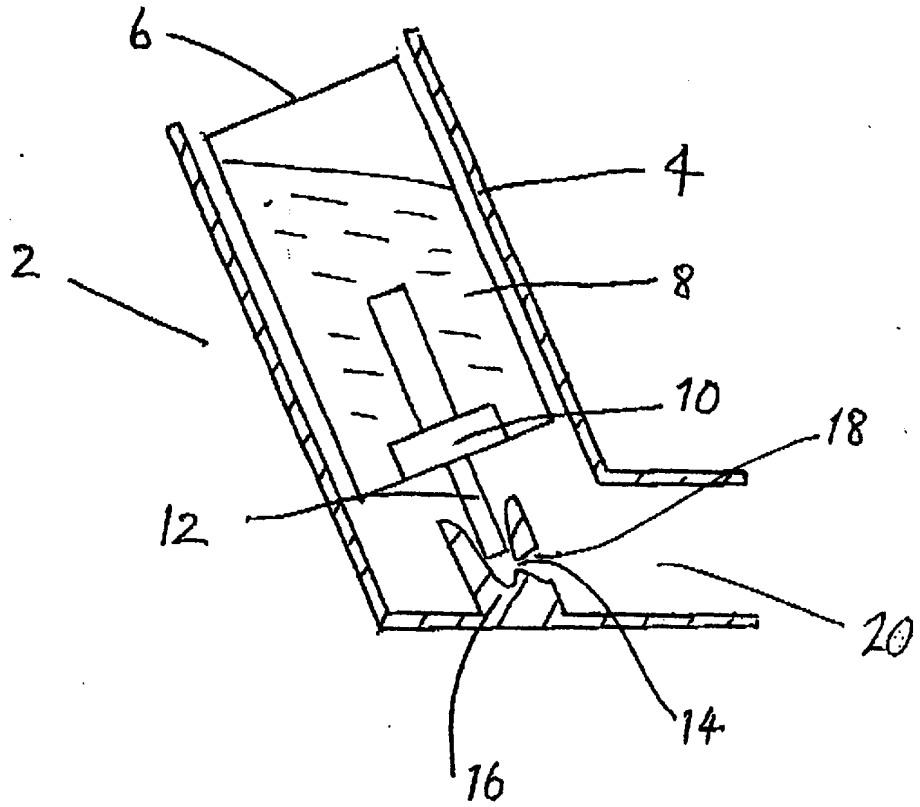
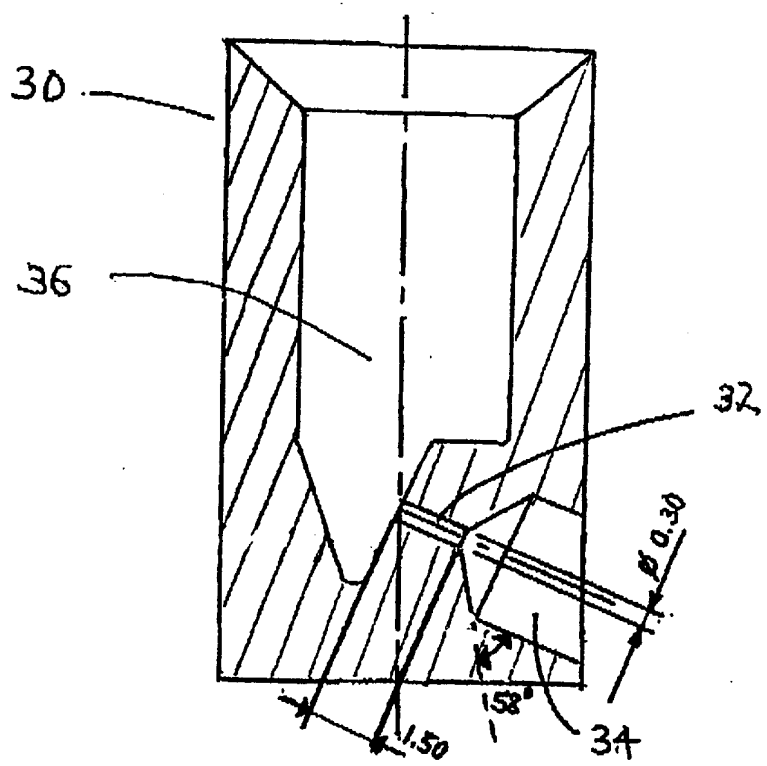


FIGURE 2



METERED DOSE INHALER

The present invention relates to actuators for aerosol propellant systems. More especially, the invention relates to an actuator for use in a metered dose inhaler.

Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves formulating the drug as a suspension or a solution in a liquefied gas propellant. The suspension/solution is stored in a sealed canister capable of withstanding the pressure required to maintain the propellant as a liquid. The suspension/solution is dispersed by activation of a dose-metering valve affixed to the canister.

A metering valve generally comprises a metering chamber that is of a set volume and is designed to administer per actuation an accurate predetermined dose of medicament. As a suspension is forced from the canister through the dose-metering valve by the high vapour pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channeling device such as a cylinder or open-ended cone. Concurrently with the activation of the aerosol dose-metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, Respiratory Drug Delivery, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

A typical MDI is illustrated in Figure 1. The MDI 2 includes an actuator body 4 in which is positioned a canister 6. The canister 6 contains a medicament 8 in solution or suspension with a low boiling point propellant. The most common propellants include the chlorofluorocarbons p-11 and p-12 or the fluorocarbons p-134a or p-227. The canister has a metering valve 10 for measuring discrete doses of the drug formulation fluid. A valve stem 12 extends from the metering valve and acts as a

conduit to pass the metered dose into an exit orifice 14 sited in a nozzle block 16 situated in the actuator body 4. The exit orifice 14 extends into an exit chamber 18 and then mouthpiece 20.

Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders that are debilitating and in some cases even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meets the specifications claimed by the manufacturer and complies with the requirements of the FDA and other regulatory authorities. Moreover, the medicament delivered by an MDI is typically directed to a specific target site in the pulmonary system. The site may include the nasal passages, the throat and/or various locations within the lungs, for example, the bronchi, bronchioles and alveolar regions.

The ability to deliver a medicament to a target area is largely dependent on the size, the velocity and the settling properties of the medicament particle. It is considered that particles having an aerodynamic diameter of less than two micrometers are optimal for deposition in the alveolar region of the lung. Particles having a diameter of between two and five micrometers are targeted to the bronchiole or bronchi regions, and particles larger than six micrometers in diameter are suitable for delivery to the laryngeal region, throat or nasal passages.

The percentage of medicament particles within a given dose of aerosolized medicament that are of the size considered optimal for deposition in a particular target area, out of the total dose, is referred to as the "fine particle mass" of the dose. The Fine Particulate Mass (FPM) (also called Fine Particle Dose) may be measured by Cascade Impaction, for example, using the equipment and method defined for pressurized Inhalers in the European Pharmacopoeia 2000, General Methods, Section 2.19.18, Apparatus D – Anderson Sizing Sampler. The FPM of an inhaled solution or suspension medicament is largely dependent on the construction and performance of the delivery system.

US-A-4992474 discloses a bronchodilating compound particularly useful in the treatment of asthma and other respiratory diseases known by the chemical name of 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol and the generic name "Salmeterol". Salmeterol as the free base and as acidic addition salts (particularly as the 1-hydroxy-2-napthalenecarboxylic acid salt also known as hydroxynapthoate or xinafoate salt), especially in aerosol form, has been accepted by the medical community as a useful treatment of asthma and is marketed under the trade mark "Serevent". Salmeterol is believed to act both by relaxing smooth muscle and inhibiting inflammation in the airways. Typically, the drug is administered as a solution, suspension or dry powder by metered dose aerosol or dispenser via the respiratory passages. Optimally therefore, the drug is targeted to the lung of the patient.

In the past, chlorofluorocarbons (CFCs) propellants (also simply known as "fluorocarbons") such as P11 and P12 have been used in combination with Salmeterol for aerosol dispensation of the drug. However, for environmental reasons, there has been a move to replace CFC's with hydrofluoroalkane (HFA) propellants such as P-134a and P-227.

Studies have shown that the performance characteristics of a drug dispensing system are sensitive to the nature and composition of the propellant used. Therefore, it is an object of the present invention to provide a delivery system for a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a fluorocarbon propellant that provides similar or improved drug delivery performance to drug suspensions comprising CFCs. Another object of the invention is to increase the FPM of the drug delivered from a metered dose inhaler. Yet another object of the invention is to produce a narrow "plume" of dispensed drug suspension from the metered dose inhaler. Another object of the invention is to reduce the rate of delivery of drug suspension to the patient from a metered dose inhaler.

Accordingly in one aspect, the invention provides a metered dose inhaler comprising a canister containing a drug suspension comprising Salmeterol, or a physiologically acceptable salt thereof, and a hydrofluoroalkane propellant, a dose-metering valve, and an actuator, the actuator having an actuator body having a nozzle block for receiving the dose-metering valve and defining therethrough a fluid flow path, the fluid flow path comprising an exit channel, wherein (i) the diameter of the exit channel at its narrowest point is between 0.2 and 0.4mm, and the length of the exit channel is between 1 and 2mm; and/or (ii) the ratio of the diameter of the exit channel at its narrowest point, to its length is between 3.5:1 and 10:1.

Preferably, the ratio is between 5:1 and 7:1.

As used herein, the term "metered dose inhaler" or "MDI" means a unit comprising a canister, a crimped cap covering the mouth of the canister, a drug metering valve situated in the cap, a metering chamber and a suitable channeling device into which the canister is fitted. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channeling device may comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in US-A-5261538.

The term “drug suspension” means Salmeterol or a physiologically acceptable salt thereof (particularly the hydroxynaphthoate salt) optionally in combination with one or more other pharmacologically active agents such as anti-inflammatory agents, analgesic agents or other respiratory drugs and optionally containing one or more excipients. The term “excipients” as used herein mean chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include

but are not limited to surfactants, preservatives, flavourings, antioxidants, anti-aggregating agents. Salmeterol or its salt thereof may be used in the form of the R-isomer or the S-isomer or a combination thereof.

The term "propellants" as used herein mean pharmacologically inert liquids with boiling points from about room temperature (25°) to about -25°C which singly or in combination exert high vapour pressure at room temperature. Upon activation of the MDI, the high vapour pressure of the propellant in the MDI forces a metered amount of drug formulation out through the metering valve whereupon the propellant very rapidly vapourises dispersing the drug particles. The propellants used in the present invention are low boiling point hydrofluoroalkanes, in particular, 1,1,1,2-tetrafluoroethane also known as propellant 134a or p134a, and 1,1,1,2,3,3,3-heptafluoro-n-propane also known as propellant 227 or p227.

Preferably, the exit channel has a diameter of 0.3mm or less and a length of at least 1.5mm.

Preferably, the diameter of the exit channel is between 0.2mm to 0.3mm, for example about 0.3mm.

Preferably, the length of the exit channel is between 1.5 and 2mm, for example about 1.5mm or about 1.8mm.

The inventors have unexpectedly discovered that the combination of dimensions presented above markedly increase the FPM for the drug suspensions defined above.

In one embodiment, the exit channel is tapered along its length such that one end of the exit channel is narrower than the other end of the exit channel.

The exit channel may have variable diameter along its length, for example the channel may include a constriction of a narrower diameter along part of its length.

In one embodiment, the drug suspension comprises Salmeterol in combination with fluticasone propionate (also known as Seretide ™) and a hydrofluoroalkane propellant.

Without wishing to be bound by theory, the inventors believe that the reduction in the diameter of the exit channel produces a finer and slower aerosol plume. The increase in length of the exit channel is believed to slow the velocity of the plume as well as produce a more focused plume with better orientation control. Small, slow droplets have a reduced tendency to deposit in the MDI device or the throat of the patient, and a greater likelihood to target the lungs as desired.

Thus, the dimensions of the exit channel according to the present invention markedly reduce the rate at which the dose of drug is dispensed to the patient (that is, the actuation time is significantly increased), increases the FPM, and therefore enhances the efficacy of the drug.

The dose-metering valve typically comprises a dose-metering chamber. In one embodiment of the invention, the benefits of an increase in FPM may be observed whereas the increase in actuation time be reduced, by the use of dose metering chambers of a volume less than the standard volume of 63 µl.

Preferably, the dose-metering chamber has a volume between 20 and 100µl, for example, 25µl, 50µl, or 63µl. Preferably, the dose-metering chamber has a volume between 50µl and 63µl.

The exit channel may intersect with an exit chamber. Typically, the angle at which the exit channel intersects with the exit chamber is between 50 and 90°, for example 58° or 90°.

In another aspect the invention provides an actuator for use in a metered dose inhaler as defined above.

In another aspect, the invention provides a method for increasing the FPM for a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant, dispensed from a metered dose inhaler comprising the use of an actuator as defined above or a metered dose inhaler as defined above.

In another aspect, the invention provides a method for increasing the FPM for a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant, dispensed from a metered dose inhaler, comprising the use of an actuator for a metered dose inhaler, the actuator having an actuator body having a nozzle block for receiving the dose-metering valve and defining therethrough a fluid flow path, the fluid flow path comprising an exit channel, wherein (i) the diameter of the exit channel at its narrowest point is between 0.2 and 0.4mm, and the length of the exit channel is between 1 and 2mm; and/or (ii) the ratio of the diameter of the exit channel at its narrowest point, to its length is between 3.5:1 and 10:1.

Preferably, the ratio is between 5:1 and 7:1.

In another aspect, the invention provides a method for the treatment, prophylaxis or diagnosis of a condition or a disease in a patient comprising administering to a patient a dose of a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant, using an actuator for a metered dose inhaler, the actuator having an actuator body having a nozzle block for receiving the dose-metering valve and defining therethrough a fluid flow path, the fluid flow path comprising an exit channel, wherein (i) the diameter of the exit channel at its narrowest point is between 0.2 and 0.4mm, and the length of the exit

channel is between 1 and 2mm; and/or (ii) the ratio of the diameter of the exit channel at its narrowest point, to its length is between 3.5:1 and 10:1.

Preferably, the ratio is between 5:1 and 7:1.

In still another aspect, the invention provides the use of a metered dose inhaler or actuator as defined above for dispensing a pharmaceutical aerosol formulation comprising a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant.

The metered dose inhalers may be prepared by methods of the art (e.g. see Byron above and US-A-5345980).

Canisters generally comprise a container capable of withstanding the vapour pressure of the HFA propellant, such as plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminium can which may optionally be anodized, lacquer-coated and/or plastics- coated, which container is closed with a metering valve. Canisters may be coated with a polymer as described in WO 96/32151, for example, a co-polymer of polyethersulphone (PES) and polytetrafluoroethylene (PTFE). Another polymer for coating that may be contemplated is FEP (fluorinated ethylene propylene). The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as, for example, low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber, neoprene, EPDM (e.g. as described in WO92/11190) and TPE (thermoplastic polymer; e.g. as described in WO95/02651). EPDM and TPE rubbers are preferred.

The drug-metering valve will preferably be manufactured of a material which is inert to and resists distortion by contents of the formulation. Usually, the valve may

consist of parts usually made of stainless steel, a pharmacologically resilient polymer, such as acetal, polyamide (e.g. Nylon^{R}), polycarbonate, polyester (e.g. polybutyleneterephthalate (PBT)), fluorocarbon polymer (e.g. Teflon^{R}) or a combination of these materials. Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

The valve typically comprises a valve body having an inlet port through which the pharmaceutical aerosol formulation may enter said valve body, an outlet port through which the pharmaceutical aerosol may exit the valve body and an open/close mechanism by means of which flow through said outlet port is controllable.

In one aspect, the valve is a slide valve wherein the open/close mechanism comprises a sealing ring and receivable by said sealing ring a valve stem having a dispensing passage, said valve stem being slidably movable within the ring from a valve-closed to a valve-open position in which the interior of the valve body is in communication with the exterior of the valve body via said dispensing passage.

In another aspect, the valve is a metering valve. The metering volume is typically from 50 to 100 μl, such as 50 μl or 63 μl. Suitably, the valve body defines a metering chamber for metering an amount of medicament formulation and an open/close mechanism by means of which the flow through the inlet port to said metering chamber is controllable. Preferably, the valve body has a sampling chamber in communication with the metering chamber via a second inlet port, said inlet port being controllable by means of an open/close mechanism thereby regulating the flow of medicament formulation into the metering chamber.

In a preferred aspect, the valve is a metering valve in which the valve body has a metering chamber, a sampling chamber and therebetween a second sealing ring within which the stem is slidably movable, the valve stem having a transfer passage such that in the valve-closed position the dispensing passage is isolated from the

metering chamber and the metering chamber is in communication with the sampling chamber via said transfer passage, and in the valve-open position the dispensing passage is in communication with the metering chamber and the transfer passage is isolated from the metering chamber.

The sealing ring may be formed by cutting a ring from a sheet of suitable material. Alternatively, the sealing ring may be formed by a moulding process such as an injection moulding, compression moulding or transfer moulding process.

Preferably the sealing ring and/or second sealing ring comprises an elastomeric material. The ring is typically resiliently deformable.

The elastomeric material may either comprise a thermoplastic elastomer (TPE) or a thermoset elastomer which may optionally be cross-linked. The sealing ring may also comprise a thermoplastic elastomer blend or alloy in which an elastomeric material is dispersed in a thermoplastic matrix. The elastomers may optionally additionally contain conventional polymer additives such as processing aids, colorants, tackifiers, lubricants, silica, talc, or processing oils such as mineral oil in suitable amounts.

Suitable thermoset rubbers include butyl rubbers, chloro-butyl rubbers, bromo-butyl rubbers, nitrile rubbers, silicone rubbers, flurosilicone rubbers, fluorocarbon rubbers, polysulphide rubbers, polypropylene oxide rubbers, isoprene rubbers, isoprene-isobutene rubbers, isobutylene rubbers or neoprene (polychloroprene) rubbers.

Suitable thermoplastic elastomers comprise a copolymer of about 80 to about 95 mole percent ethylene and a total of about 5 to about 20 mole percent of one or more comonomers selected from the group consisting of 1-butene, 1-hexene, and 1-octene as known in the art. Two or more such copolymers may be blended together to form a thermoplastic polymer blend.

Another suitable class of thermoplastic elastomers are the styrene-ethylene/ butylene-styrene block copolymers. These copolymers may additionally comprise a polyolefin (e.g. polypropylene) and a siloxane.

Thermoplastic elastomeric material may also be selected from one or more of the following: polyester rubbers, polyurethane rubbers, ethylene vinyl acetate rubber, styrene butadiene rubber, copolyether ester TPE, olefinic TPE, polyester amide TPE and polyether amide TPE.

Other suitable elastomers include ethylene propylene diene rubber (EPDM). The EPDM may be present on its own or present as part of a thermoplastic elastomer blend or alloy, e.g. in the form of particles substantially uniformly dispersed in a continuous thermoplastic matrix (e.g. polypropylene or polyethylene). Commercially available thermoplastic elastomer blend and alloys include the SANTOPRENE™ elastomers. Other suitable thermoplastic elastomer blends include butyl-polyethylene (e.g. in a ratio ranging between about 2:3 and about 3:2) and butyl-polypropylene.

Materials of manufacturing of the metering chamber and/or the valve stem may desirably be fluorinated, partially fluorinated or impregnated with fluorine containing substances in order to resist drug deposition. For example, any parts of the valve which contact the pharmaceutical aerosol suspension may be coated with materials such as fluoropolymer materials which reduce the tendency of medicament to adhere thereto. Suitable fluoropolymers include polytetrafluoroethylene (PTFE) and fluoroethylene propylene (FEP). Any movable parts may also have coatings applied thereto which enhance their desired movement characteristics. Frictional coatings may therefore be applied to enhance frictional contact and lubricants used to reduce frictional contact as necessary.

Preferably, the sealing ring and/or the second sealing ring additionally comprises lubricant material. Suitably, the sealing ring and/or the second sealing ring comprises up to 30%, preferably from 5 to 20% lubricant material.

Preferably, the stem comprises lubricant material. Suitably, the valve stem comprises up to 30%, preferably from 5 to 20% lubricant material.

The term 'lubricant' herein means any material which reduces friction between the valve stem and seal. Suitable lubricants include silicone oil or a fluorocarbon polymer such as polytetrafluoroethane (PTFE) or fluoroethylene propylene (FEP).

Lubricant can be applied to the stem, sealing ring or second sealing ring by any suitable process including coating and impregnation, such as by injection or a tamponage process.

Suitable valves are commercially available, for example from Valois SA, France (e.g. DF10, DF30, DF60), Bespak Plc, UK (e.g. BK300, BK356, BK357) and 3M-Neotechnic Ltd UK (e.g. Spraymiser (trade name)).

The pharmaceutical formulations for use in the canisters of the invention contain no components that provoke the degradation of stratospheric ozone. In particular the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3.

The propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon for example propane, n-butane, isobutane, pentane and isopentane or a dialkyl ether for example dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations that are free or substantially free of volatile adjuvants are preferred. In certain cases, it may be desirable to include appropriate amounts of

water, which can be advantageous in modifying the dielectric properties of the propellant.

A surfactant may also be employed in the aerosol formulation. Examples of conventional surfactants are disclosed in EP 372777. The amount of surfactant employed is desirable in the range 0.0001% to 50% weight to weight ratio relative to the medicament, in particular, 0.05 to 5% weight to weight ratio. Preferred surfactants are lecithin, oleic acid and sorbitan trioleate. Preferred formulations, however, are free or substantially free of surfactant.

Pharmaceutical formulations may contain 0.0001 to 50% w/w, preferably 0.001 to 20%, for example 0.001 to 1% of sugar relative to the total weight of the formulation. Generally the ratio of medicament to sugar falls within the range of 1:0.01 to 1:100 preferably 1:0.1 to 1:10. Typical sugars that may be used in the formulations include, for example, sucrose, lactose and dextrose, preferably lactose, and reducing sugars such as mannitol and sorbitol, and may be in micronised or milled form.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 to 5% w/w, especially 0.01 to 1.0% w/w, of medicament relative to the total weight of the formulation.

It will be appreciated by those skilled in the art that the drug suspensions according to the invention may, if desired, contain Salmeterol or a salt thereof in combination with one or more other pharmaceutically active agents. Such medicaments may be selected from any suitable drug useful in inhalation therapy. Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (eg s the sodium salt), ketotifen or nedocromil (eg as the sodium salt); antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti- inflammatories, e.g., beclomethasone (eg as the dipropionate

ester), fluticasone (eg as the propionate ester), flunisolide, budesonide, rofleponide, mometasone eg as the furoate ester), ciclesonide, triamcinolone (eg as the acetonide) or 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (eg as free base or sulphate), salmeterol (eg as xinafoate), ephedrine, adrenaline, fenoterol (eg as hydrobromide), formoterol (eg as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (eg as acetate), reproterol (eg as hydrochloride), rimiterol, terbutaline (eg as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone; adenosine 2a agonists, eg 2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (e.g. as maleate); α_4 integrin inhibitors eg (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy) acetyl]amino}pentanoyl)amino] propanoic acid (e.g as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (eg as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; vaccines, diagnostics, and gene therapies

It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimize the activity and/or stability of the medicament and/or to minimize the solubility of the medicament in the propellant. It will further be clear to a person skilled in the art that where appropriate, the medicaments may be used in the form of a pure isomer, for example the R- or S-isomer, or a combination of isomers.

Particularly preferred drug suspensions may contain Salmeterol or a physiologically acceptable salt thereof in combination with an anti-inflammatory steroid such as

fluticasone (e.g. as the propionate ester), or physiologically acceptable solvates thereof.

Particularly preferred formulations for use in the canisters of the present invention comprise a medicament and a C_{1-4} hydrofluoroalkane particularly 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-n-heptafluoropropane or a mixture thereof as propellant.

Preferred formulations are free or substantially free of formulation excipients. Thus, preferred formulations consist essentially of (or consist of) the medicament and the selected propellant.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquified propellant is pressure filled through the charge vessel into a manufacturing vessel. The drug suspension is mixed before re-circulation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister, followed by an aliquot of pure propellant. Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channeling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose inhalers are designed to

deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1, 2, 3 or 4 puffs each time. Each valve actuation, for example, may deliver 5μg, 50μg, 100μg, 200μg or 250μg of a medicament. Typically, each filled canister for use in a metered dose inhaler contains 60, 100, 120 or 200 metered doses or puffs of medicament; the dosage of each medicament is either known or readily ascertainable by those skilled in the art.

A still further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, or chronic obstructive poulmonary disorder (COPD) which comprises administration by inhalation of an effective amount of an aerosol formulation as herein described from a metered dose inhaler of the present invention.

The invention will now be described by reference to the accompanying drawing, Figure 2, which illustrates an actuator in accordance with one embodiment of the invention.

Figure 2 shows an actuator nozzle block 30. The nozzle block 30 includes an exit channel 32 that exits into an exit chamber 34. The exit channel is 0.3mm in diameter and 1.5mm in length. The exit channel intersects with the exit chamber 34 at an angle of 58°. A metered dose inhaler (not shown) comprising an actuator having the

nozzle block of Figure 2, comprises a canister (not shown) of drug suspension comprising Salmeterol and a hydrofluoroalkane propellant, the canister having a dose-metering valve and valve stem. The canister may be inserted into the nozzle block body 36. When a dose is dispensed, the suspension will be released from the valve stem and via the exit channel 32 to the exit chamber 34 for dispensation to the patient.

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto which will be within the ordinary skill of the person skilled in the art.

Claims:-

1. A metered dose inhaler having a canister containing a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant, a dose-metering valve, and an actuator, the actuator having an actuator body having a nozzle block for receiving the dose-metering valve and defining therethrough a fluid flow path, the fluid flow path comprising an exit channel, wherein (i) the diameter of the exit channel at its narrowest point is between 0.2 and 0.4mm, and the length of the exit channel is between 1 and 2mm; and/or (ii) the ratio of the diameter of the exit channel at its narrowest point, to its length is between 3.5:1 and 10:1.

2. A metered dose inhaler as claimed in claim 1 wherein the ratio is between 5:1 and 7:1.

3. A metered dose inhaler as claimed in claim 1or claim 2 wherein the exit channel has a diameter of 0.3mm or less and a length of at least 1.5mm.

4. A metered dose inhaler as claimed in claim 3 wherein the diameter of the exit channel is between 0.2mm to 0.3mm.

5. A metered dose inhaler as claimed in claim 4 wherein the diameter of the exit channel is about 0.3mm.

6. A metered dose inhaler as claimed in any one of claims 3 to 5 wherein the length of the exit channel is between 1.5mm and 2mm.

7. A metered dose inhaler as claimed in claim 6 wherein the length of the exit channel is about 1.5mm.

8. A metered dose inhaler as claimed in claim 6 wherein the length of the exit channel is about 1.8mm.

9. A metered dose inhaler as claimed in any one of the preceding claims wherein the exit channel is tapered along its length such that one end of the exit channel is narrower than the other end of the exit channel.

10. A metered dose inhaler as claimed in any one of the preceding claims wherein the exit channel has variable diameter along its length.

11. A metered dose inhaler as claimed in claim 10 wherein the channel includes a constriction of a narrower diameter along part of its length.

12. A metered dose inhaler as claimed in any one of the preceding claims wherein the drug suspension comprises Salmeterol in combination with fluticasone propionate; and a hydrofluoroalkane propellant.

13. A metered dose inhaler as claimed in any one of the preceding claims wherein the hydrofluoroalkane propellant is selected from a C_{1-4} hydrofluoroalkane.

14. A metered dose inhaler as claimed in claim 13 wherein the hydrofluoroalkane propellant is selected from 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-n-heptafluoropropane or a mixture thereof.

15. A metered dose inhaler as claimed in any one of the preceding claims wherein the dose-metering valve comprises a dose-metering chamber and the dose-metering chamber has a volume between 20µl and 100µl.

16. A metered dose inhaler as claimed in claim 15 wherein the dose-metering chamber has a volume of 63µl.

17. A metered dose inhaler as claimed in claim 15 wherein the dose-metering chamber has a volume of 50µl.

18. A metered dose inhaler as claimed in claim 15 wherein the dose-metering chamber has a volume of 25µl.

19. A metered dose inhaler as claimed in any one of the preceding claims wherein the exit channel intersects with an exit chamber.

20. A metered dose inhaler as claimed in claim 19 wherein the angle at which the exit channel intersects with the exit chamber is between 50 and 90°.

21. A metered dose inhaler as claimed in claim 20 wherein the angle at which the exit channel intersects with the exit chamber is 58°.

22. A metered dose inhaler as claimed in claim 20 wherein the angle at which the exit channel intersects with the exit chamber is 90°.

23. A metered dose inhaler substantially as described hereinabove and with reference to the accompanying drawings.

24. An actuator for use in a metered dose inhaler as claimed in any one of the preceding claims.

25. An actuator substantially as described hereinabove and with reference to the accompanying drawings.

26. A method for increasing the FPM for a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant dispensed from a metered dose inhaler comprising the use of an actuator

as claimed in claim 24 or 25 or a metered dose inhaler as claimed in any one of claims 1 to 23.

27. A method for increasing the FPM for a drug suspension comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant dispensed from a metered dose inhaler, comprising the use of an actuator for a metered dose inhaler, the actuator comprising an actuator body having a nozzle block for receiving the dose metering valve and defining therethrough a fluid flow path, the fluid flow path comprising an exit channel, wherein (i) the diameter of the exit channel at its narrowest point is between 0.2 and 0.4mm, and the length of the exit channel is between 1 and 2mm; and/or (ii) the ratio of the diameter of the exit channel at its narrowest point, to its length is between 3.5:1 and 10:1.

28. A method substantially as described hereinabove.

29. The use of a metered dose inhaler as claimed in any one of claims 1 to 23 and/or an actuator as claimed in claim 24 or 25 for dispensing a pharmaceutical aerosol formulation comprising Salmeterol (or a physiologically acceptable salt thereof) and a hydrofluoroalkane propellant.

Application No: GB 0020978.3
Claims searched: 1-23, 26-29

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Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T):

Int Cl (Ed.7): A61M15/00, A61K9/00, A61K9/12, B05B11/00

Other: Online PAJ/WPI/EPODOC

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
E/A	WO01/64275 A1	(GLAXO GROUP LIMITED) see page 13 lines 13-20; page 15 lines 19-28; page 16 lines 1-7; page 17 lines 1-6 and 15-18.	
E/X	WO01/47493 A1	(GLAXO GROUP LIMITED) see whole document and in particular page 4 lines 13-30; page 5 lines 1-4; page 6 lines 27-30; page 12 line 23-page 13 line 4; page 16 lines 24-25.	1, 3-7, 9-12, 14-17, 19, 26, 27 and 29
A	WO00/30607 A1	(CHIESI FARMACEUTICI SPA) see whole document	
A	WO96/32150 A1	(GLAXO WELLCOME INC) see page 5 line 29-page 6 line 2.	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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